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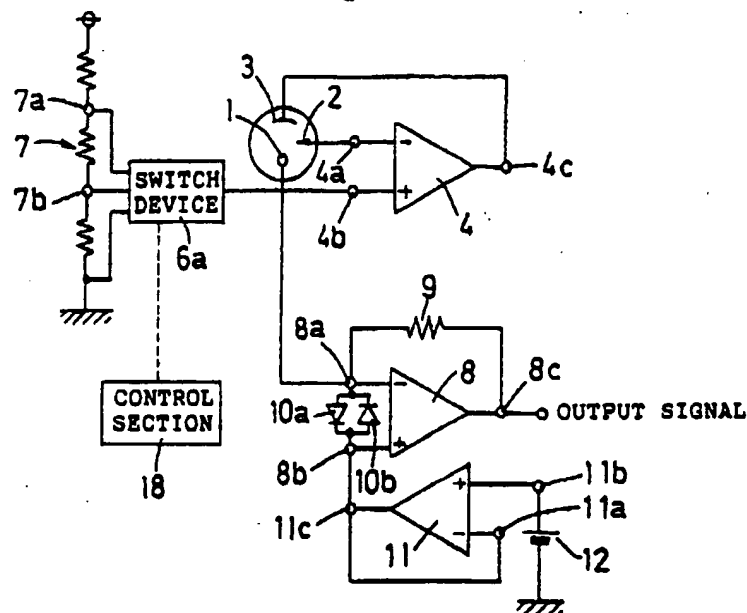
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(54) Method and apparatus for reviving an electrode of a biosensor.

(57) After a reverse bias is applied between a working electrode and a counter electrode or a reference electrode, a forward bias higher than a forward measurement bias is applied between the working electrode and the counter electrode or the reference electrode before the forward measurement bias is applied. This reduces a time period before an actual measuring operation is possible.

Fig.1



EP 0 415 393 A1

METHOD AND APPARATUS FOR REVIVING AN ELECTRODE OF A BIOSENSOR

The present invention relates to methods and apparatus for reviving an electrode of a biosensor, and more particularly to methods and apparatus for reviving an electrode of a biosensor by supplying a bias having a different polarity from the measurement bias polarity to the electrode before a measuring operation is started.

5 It is known that a physiologically active substance is capable of selectively detecting a very complicated organic compound, protein or the like with high sensitivity. With attention directed to this characteristic, research has been made in various biosensors.

A typical biosensor having an electrode unit and a physiologically active substance fixed thereon is proposed. The biosensor is used for detecting the existence of an object substance, the relative or active
10 quantity of the object substance and the like based on an electrical signal output from the electrode unit corresponding to the biological reaction of the object substance, under the condition that a predetermined forward bias is applied to the electrode unit. For example, the electrode unit has a working electrode made of platinum and a counter electrode made of silver. An enzyme-immobilized membrane is fixed onto the electrode unit. When the object substance is to be measured, hydrogen peroxide is generated through an
15 enzyme reaction of the object substance. Then the generated hydrogen peroxide reaches the surface of the electrode unit through a hydrogen peroxide penetration membrane. The electrode unit outputs an electrical signal corresponding to the quantity of hydrogen peroxide that reaches it. The existence of the object substance, the relative or active quantity of the object substance and the like are detected based on the electrical signal. Concretely, the working electrode has a forward bias of 0.6 volts applied with respect to
20 the counter electrode.

In the biosensor described above, an interfering layer such as an oxidized layer and the like which interferes with electrical signals is generated on the working electrode, and the activity of the working electrode is lowered as the object substance measuring operation is continued with the forward bias being applied to the electrode unit. It is proposed that a reverse bias is accordingly applied to the electrode unit
25 (the working electrode has a reverse bias of about -0.6 volts applied with respect to the counter electrode, corresponding to the concrete example) after one or more measuring is performed, within the time period in which the measurement is not performed, so as to remove the interfering layer. Then the activity of the working electrode is revived. The level of the output signal from the electrode unit is raised to the original level. (Refer to Japanese Patent Laid Open Sho 60-155959).

30 Lowered measuring sensitivity is recovered by applying the predetermined reverse bias voltage to the electrode unit within the time period in which the measurement is not performed, as is described above, then measuring with high sensitivity can be performed again.

In the reviving apparatus described above, a constant-voltage for reviving (reverse bias) is applied between the working electrode and the counter electrode. The oxidized layer on the working electrode is
35 reduced, hydrogen, hydrogen ions and the like are accordingly generated. When a constant-voltage for measurement (forward bias) is applied between the working electrode and the counter electrode, a diffusion current flows depending upon the generated hydrogen, hydrogen ions and the like.

As a result, the electrical signal provided for measuring is affected by lowering, by the diffusion current, so as to remarkably lower measuring accuracy just after the constant-voltage for measurement is applied
40 between the working electrode and the counter electrode. When the measurement is performed after the diffusion current is sufficiently lowered, sufficient measuring accuracy is obtained, but a remarkably long waiting time period (for example, 1-2 minutes) is needed.

The same disadvantages as above arises for a biosensor having a reference electrode in addition to the working electrode and the counter electrode.

45 It is an object of the present invention to shorten the time period between performing a reviving operation for an electrode unit to when it is possible to start a measuring operation for an object substance.

This present invention first applies a predetermined reverse bias to a working electrode for a predetermined time period, then, applies forward bias higher than a forward measurement bias to the working electrode for a predetermined time period, then, applies the forward measurement bias to the
50 working electrode.

In this reviving method, an interfering layer on the working electrode which interferes with the turning on of electricity is reduced and the activity of the working electrode is revived by applying the reverse bias to the working electrode. Substances generated through reduction of the interfering layer are moved to one of the electrodes at high speed by applying the forward bias higher than the forward measurement bias to the working electrode. The substances are rapidly consumed, accordingly, when the forward bias is applied to

the working electrode. As a result, a time period between performing a reviving operation for an electrode unit to when it is possible to start a measuring operation for an object substance with a predetermined accuracy maintained, is remarkably shortened.

5 The time period for applying the higher bias to the working electrode may be nearly equal to the time period for applying the reverse bias to the working electrode.

It is preferred that the predetermined reverse bias is a reverse bias which is gradually increased until its absolute value reaches a predetermined value. Damage of a membrane fixed on the surface of the electrode unit, effected by current is remarkably reduced.

10 It is also preferred that the higher forward bias is a forward bias which is gradually increased until its absolute value reaches a higher predetermined value than the forward bias for measuring. Damage of the membrane fixed on the surface of the electrode unit, effected by current is remarkably reduced.

It is further preferred that the predetermined reverse bias is a reverse bias which is gradually increased until its absolute value reaches a predetermined value, and the higher forward bias is a forward bias which is gradually increased until its absolute value reaches a predetermined value higher than the forward measurement bias. Damage of the membrane fixed on the surface of the electrode unit, effected by current is remarkably reduced.

This present invention comprises;

reviving voltage applying means for applying voltage for reviving to a working electrode;

measurement voltage applying means for applying voltage for measuring to the working electrode;

20 higher voltage applying means for applying a higher voltage than the voltage for measuring to the working electrode;

selection means for sequentially selecting a condition under which to apply a voltage for reviving to the working electrode from the reviving voltage applying means, a condition under which to apply a higher voltage to the working electrode from the higher voltage applying means, and a condition under which to

25 apply a voltage for measuring to the working electrode from the measurement voltage applying means, when measuring an operation is to be performed.

In this reviving apparatus, the condition of applying voltage for reviving to the working electrode by the reviving voltage applying means and the condition of applying the higher voltage to the working electrode by the higher voltage applying means are selected in this order by the selection means, before an actual

30 measuring operation is started. First, the interfering layer on the surface of the working electrode is removed. After the interfering layer has been removed, substances generated through removal of the interfering layer are moved to one of the electrodes at high speed by applying the higher forward bias to the working electrode. The substances are rapidly consumed when the forward bias is applied to the working electrode. As a result, after a short time period from when a reviving operation for an electrode unit

35 has passed, a measuring operation for an object substance can be started with a predetermined accuracy maintained.

It is preferred that the reviving apparatus further comprises a first time constant means for applying a predetermined time constant to the reviving voltage. Damage of a membrane fixed on a surface of an

40 electrode unit, effected by current is remarkably reduced.

It is also preferred that the reviving apparatus further comprises a second time constant means for applying a predetermined time constant to the higher voltage. Damage of a membrane fixed on a surface of an electrode unit, effected by current is remarkably reduced.

It is further preferred that the reviving apparatus further comprises a first time constant means for applying a predetermined time constant to the reviving voltage, and a second time constant means for

45 applying a predetermined time constant to the higher voltage. Damage of a membrane fixed on a surface of an electrode unit, effected by current is remarkably reduced.

More specifically, the interfering layer can easily be removed by a reduction operation because the reviving operation is an operation to remove the interfering layer formed on the working electrode, and the interfering layer is generated by oxidization. When the interfering layer is removed, hydrogen, hydrogen

50 ions and the like are inevitably generated through removal of the interfering layer. The generated substances diffuse when the voltage for measuring is applied to the working electrode. As a result, concentration measuring of an object substance with high accuracy is performed only after the diffusion current is sufficiently lowered. Concretely, when the forward measurement bias is determined to be 0.75 volts and the reverse bias for reviving is determined to be -1 volt, the diffusion current is sufficiently lowered

55 only after 1-2 minutes after removal of the interfering layer. The disadvantage of having to wait a long time period until actual measuring can be started, arises.

On the contrary, in the present invention, substances generated through removal of the interfering layer are moved to one of the electrodes at high speed because the higher voltage is applied to the working

electrode before the measurement voltage is applied to the working electrode. The substances are sufficiently close to one of the electrodes, accordingly, when the measurement voltage is applied to the working electrode, thereby the substances are rapidly consumed when the measurement voltage is applied to the working electrode. As a result, a time period between removal of the interfering layer to when it is possible to start the concentration measuring of an object substance with high accuracy is remarkably shortened.

Figures 4 are diagrams useful in understanding the operation described above. Figs. 4(A1) to fig. 4(A3) correspond to a conventional case, while figs. 4(B1) to fig. 4(B3) correspond to this present invention.

As is illustrated in figs 4(A1) and 4(B1), the same quantity of generated substances exist between the working electrode and the reference electrode when the interfering layer is removed. Then, in the conventional case, only a fairly small moving force toward the working electrode acts on the generated substances as is illustrated in fig 4(A2), thereby the time period for consuming a predetermined quantity of the generated substances is lengthened. That is, the generated substances are not so close to the working electrode as is illustrated in fig. 4(A3) after a predetermined time period has passed, thereby a long time period is needed for most of the generated substances to reach the working electrode and be consumed. On the contrary, in this present invention, a fairly large moving force toward the working electrode acts on the generated substances as is illustrated in fig. 4(B2), thereby the generated substances are fairly close to the working electrode when a time period equal to the above described time period has passed, as is illustrated in fig. 4(B3). Thereafter, the same moving force as in the conventional case acts on the generated substances. A time period for consuming a predetermined quantity of the generated substances is reduced because the generated substances are already close to the working electrode. As a result, the time period between removal of the interfering layer to when it is possible to start actual measuring is remarkably shortened. A biosensor having three electrodes is illustrated in figs. 4. A biosensor having two electrodes, excluding the reference electrode, is similar to the biosensor having three electrodes.

These and other objectives, features and advantages of the present invention will be more readily understood upon consideration of the present invention, taken in conjunction with the accompanying drawings.

Figure 1 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a first embodiment of the present invention;

Figure 2 is a vertical sectional view of the center portion of an electrode unit;

Figures 3(A) and 3(B) are diagrams showing variations of bias voltage and current when the electrode unit is revived;

Figures 4(A1), 4(A2), 4(A3), 4(B1), 4(B2), and 4(B3) are diagrams showing movement of substances generated through reviving of the electrode unit;

Figure 5 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a second embodiment of the present invention;

Figure 6 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a third embodiment of the present invention;

Figures 7(A) and 7(B) are diagrams showing variations of bias voltage and current when the electrode unit is revived;

Figure 8 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a fourth embodiment of the present invention.

Fig. 1 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a first embodiment of the present invention.

The apparatus revives an electrode unit having three electrodes, such as a working electrode 1 made of platinum, a reference electrode 2 and a counter electrode 3, both made of silver.

The reference electrode 2 and the counter electrode 3 are connected to an inverting input terminal 4a and an output terminal 4c of an operational amplifier 4, respectively. A non-inverting input terminal 4b of the operational amplifier 4 is selectively connected to a high voltage tap 7a, a low voltage tap 7b or ground of a voltage divider 7 having resistances by means of a switch device 6a. An inverting input terminal 8a of a current/voltage converting operational amplifier 8 for providing measurement signal is connected to the working electrode 1. A current/voltage converting resistance 9 is connected between an output terminal 8c and the inverting input terminal 8a of the current/voltage converting operational amplifier 8. Diodes 10a and 10b are connected in parallel and in reverse polarity with respect to one another between the inverting input terminal 8a and a non-inverting input terminal 8b of the current/voltage converting operational amplifier 8. A DC power source 12 for measuring is connected to a non-inverting input terminal 11b of a buffer amplifier 11. An output terminal 11c of the buffer amplifier 11 is connected directly to an inverting input terminal 11a of the buffer amplifier 11. The output terminal 11c of the buffer amplifier 11 is connected to the non-

inverting input terminal 8b of the current/voltage converting operational amplifier 8. The DC power source 12 is used for applying a forward bias of 0.75 volts to the working electrode 1. The high voltage tap 7a and the low voltage tap 7b are used for applying biases of -1 volt and 1 volt respectively, to the working electrode 1. A control section 18, provided as a selection means, is used to control the operation of the switch device 6a.

Fig. 2 is a vertical sectional view of the center portion of an electrode unit to which the reviving apparatus is applied.

The working electrode 1 is provided at a predetermined position in an electrode unit body 13. The ring shaped reference electrode 2 and the ring shaped counter electrode 3, both electrodes 2 and 3 surrounding the periphery of the working electrode 1, are provided in the electrode unit body 13 in this order. The electrode unit body 13 has a convex surface on the side on which the working electrode 1, the reference electrode 2 and the counter electrode 3 are provided. A hydrogen peroxide selective penetration membrane 14, a glucose oxidase immobilized membrane (hereinafter referred to as GOD immobilized membrane) 15 and a diffusion-limiting membrane 16 made of polyvinyl acetate and the like are provided in this order to fit the convex surface of the electrode unit body 13. Terminals 17 for supplying output signals are provided in the electrode unit body 13. The terminals 17 are connected to the working electrode 1, the reference electrode 2 and the counter electrode 3, respectively.

The operation of the sensor for measuring glucose concentrations having the arrangement described above is as follows.

When measuring of glucose concentrations is carried out, the non-inverting input terminal 4b of the operational amplifier 4 is connected to the high voltage tap 7a of the voltage divider 7 by operating the switch device 6a. Then, a constant voltage for reviving (for example the constant voltage of -1 volt) is applied between the working electrode 1 and the reference electrode 2 (Refer to a region R1 in figs. 3(A) and 3(B)).

In this condition, current flows to reduce interfering substances which are formed on a surface of the working electrode 1. The interfering substances are completely removed and activity of the working electrode 1 is revived by continuing to apply the constant voltage for reviving between the electrodes 1 and 2 for a fairly short time period (for example a time period of about 4 seconds). When the interfering substances are completely removed, hydrogen, hydrogen ions and the like are disposed between the working electrode 1 and the reference electrode 2.

Thereafter, the non-inverting input terminal 4b of the operational amplifier 4 is connected to the low voltage tap 7b of the voltage divider 7 by operating the switch device 6a. Then, a higher voltage (for example the higher voltage of 1 volt) higher than a measurement voltage is applied between the working electrode 1 and the reference electrode 2 (Refer to a region R2 in figs. 3(A) and 3(B)).

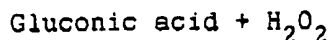
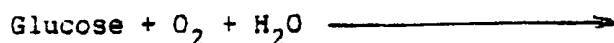
In this condition, a large moving force acts on the floating hydrogen, hydrogen ions and the like to move them toward the working electrode 1. Most hydrogen, hydrogen ions and the like are moved close to the working electrode 1 by applying a high voltage between the working electrode 1 and the reference electrode 2 for a fairly short time period (for example, a time period of about 5 seconds).

Thereafter, the non-inverting input terminal 4b of the operational amplifier 4 is connected to ground of the voltage divider 7 by operating the switch device 6a. Then, a predetermined voltage (for example a voltage of 0.75 volts) is applied as a forward bias to the working electrode 1 on the basis of the reference electrode 2. The hydrogen, hydrogen ions and the like are consumed within a short time period, then glucose concentrations may be measured. The time period between removal of interfering substances to when measuring is permitted 1-2 minutes in conventional reviving apparatus, while the time period is reduced to about 30-45 seconds in this embodiment.

After reviving is finished, a signal corresponding to the concentration of glucose is output as follows by dropping an object solution onto the electrode unit.

The dropped object solution is guided to the GOD immobilized membrane 15 with limited penetration by the glucose to some degree, by the diffusion-limiting membrane 16. Then, the following reaction takes place:

GOD



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10 Hydrogen peroxide, the quantity of which corresponds to concentration of existing glucose, is accordingly generated. The generated hydrogen peroxide is guided to the surface of the working electrode 1 which is revived to have sufficient activity, through the hydrogen peroxide selective penetration membrane 14. The forward bias is kept applied to the working electrode 1. An oxydation reaction is carried out on the surface of the working electrode 1 and current corresponding to the amount of hydrogen peroxide flows in through the working electrode 1. The current is applied to the inverting input terminal 8a of the current/voltage converting operational amplifier 8, then a voltage signal is output from the output terminal 8c of the current/voltage converting operational amplifier 8. The voltage signal is generated by adding an offset voltage caused by the forward bias and a voltage signal being proportional to the current.

15 Thereafter, only the voltage signal proportional to the current is extracted, then the extracted voltage signal is differentiated to obtain a first-order differential value, then a peak value of the first-order differential value is detected. Finally, a glucose concentration detection signal with high accuracy is obtained by performing the necessary operations.

20 Fig. 5 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a second embodiment of the present invention.

25 Different points from the first embodiment are as follows,

- (1) an electrode unit having two electrodes, one is the working electrode 1 made of platinum while another, the counter electrode 3 made of silver, is used for being revived, and
- (2) the counter electrode 3 is directly connected to the switch device 6a by omitting the operational amplifier 4.

30 In this embodiment, reviving for an electrode unit having two electrodes can be performed. Also, the time period between removal of an interfering substances to when it is possible to start actual measuring can be shortened.

Fig. 6 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a third embodiment of the present invention.

35 Different points from the first embodiment are as follows,

- (1) the non-inverting input terminal 4b of the operational amplifier 4 is connected to ground through a condenser 5,
- (2) the non-inverting input terminal 4b is selectively connected to the high voltage tap 7a and the low voltage tap 7b of the voltage divider 7 through a resistance 5a and the switch device 6a.

40 In this embodiment, bias voltages are increased in absolute value (refer to fig. 7(A)) based on a time constant (for example, a time constant of 0.5 seconds). The time constant is determined based on the resistance 5a and the condenser 5. As a result, current undershoots and overshoots are remarkably suppressed as is illustrated in fig. 7(B). That is, an excessive current is securely prevented from flowing. Damage to a membrane or membranes fixed on the surface of the electrode unit, effected by current is remarkably reduced, accordingly. As a result, the life of a membrane or membranes is extended up to about one year while the life of a membrane or membranes applied in the conventional reviving apparatus is about one month. The life is a time period when the penetration ratio of the hydrogen peroxide selective penetration membrane increases by 10 %.

45 Fig. 8 is an electronic circuit diagram of an electrode reviving apparatus in accordance with a fourth embodiment of the present invention.

50 Different points from the third embodiment are as follows,

- (1) an electrode unit having two electrodes, one is the working electrode 1 made of platinum while another, the counter electrode 3 made of silver, is used for being revived, and
- (2) the counter electrode 3 is directly connected to the switch device 6a by omitting the operational amplifier 4.

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In this embodiment, reviving for an electrode unit having two electrodes can be performed. Also, the time period between removal of interfering substances to when it is possible to start actual measuring can be shortened. Furthermore, damage to a membrane or membranes fixed on the surface of the electrode

unit, effected by current is remarkably reduced.

This invention is not limited to the foregoing embodiments. Preferably, the voltage for reviving and higher voltage are changed. Preferably, the time period for applying voltage is changed corresponding to the voltage value. Preferably, the reviving method and apparatus are applicable to apparatus for measuring
 5 concentrations of substances other than glucose. Preferably, a programmable power source which varies the output voltage under control by a microcomputer, is employed instead of the time constant circuit comprising the resistance 5a and the condenser 5.

The terms and expressions which have been employed here are used as terms of description and not of limitations, and there is no intention, in the use of such terms and expressions of excluding equivalents of
 10 the features shown and described, or portions thereof, it being recognized that various modifications are possible within the scope of the invention as claimed.

Claims

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1. A method for reviving an electrode unit of a biosensor which includes a working electrode (1) and a counter electrode (3), and which measures a concentration of an object substance based upon an electrical signal generated between the working electrode (1) and the counter electrode (3) when a predetermined forward measurement bias is applied to the working electrode (1) on which a physiologically active
 20 substance is placed, the electrical signal being generated based upon a biological reaction of the object substance, characterized in that;

(1) applying a predetermined reverse bias to the working electrode (1) for a first predetermined time period; and

(2) applying a higher forward bias than the forward measurement bias to the working electrode (1) for a
 25 second predetermined time period before the forward measurement bias is applied to the function electrode (1).

2. A method as set forth in claim 1, wherein the second predetermined time period is nearly equal to the first predetermined time period

3. A method as set forth in claim 1, wherein the predetermined reverse bias is a reverse bias which is
 30 gradually increased until its absolute value reaches a predetermined value.

4. A method as set forth in claim 1, wherein the higher forward bias is a forward bias which is gradually increased until its absolute value reaches a predetermined value which is higher than the forward measurement bias.

5. A method as set forth in claim 1, wherein the predetermined reverse bias is a reverse bias which is
 35 gradually increased until its absolute value reaches a predetermined value, and the higher forward bias is a forward bias which is gradually increased until its absolute value reaches a predetermined value which is higher than the forward measurement bias.

6. An apparatus for reviving an electrode unit of a biosensor which includes a working electrode (1) and a counter electrode (3), and which measures a concentration of an object substance based upon an electrical
 40 signal generated between the working electrode (1) and the counter electrode (3) when a predetermined forward measurement bias is applied to the working electrode (1) on which a physiologically active substance is placed, said electrical signal being generated based upon a biological reaction of said object substance, characterized in that;

reviving voltage applying means (4, 6a, 7a) for applying a reviving voltage to said working electrode (1);

45 measurement voltage applying means (4, 6a) for applying a measurement voltage to said working electrode (1);

higher voltage applying means (4, 6a, 7b) for applying a voltage higher than the measurement voltage to said working electrode (1); and

selection means (18) for sequentially selecting a condition under which to apply a reviving voltage to said
 50 working electrode (1) from said reviving voltage applying means (4, 6a, 7a), a condition under which to apply a higher voltage to said working electrode (1) from said higher voltage applying means (4, 6a, 7b), and a condition under which to apply a measurement voltage to said working electrode (1) from said measurement voltage applying means (4, 6a), when a measuring operation is to be performed.

7. An apparatus as set forth in claim 6, further comprising a first time constant means (5, 5a) for controlling
 55 a reviving voltage supplied by said reviving voltage applying means (4, 6a, 7a) according to a predetermined time constant.

8. An apparatus as set forth in claim 6, further comprising a second time constant means (5, 5a) for controlling a higher voltage supplied by said higher voltage applying means (4, 6a, 7b) according to a

predetermined time constant.

9. An apparatus as set forth in claim 6, further comprising a first time constant means (5, 5a) for controlling a reviving voltage applied by said reviving voltage applying means (4, 6a, 7a) according to a predetermined time constant, and a second time constant means (5, 5a) for controlling a higher voltage applied by said
5 higher voltage applying means (4, 6a, 7b) according to a predetermined time co

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Fig.1

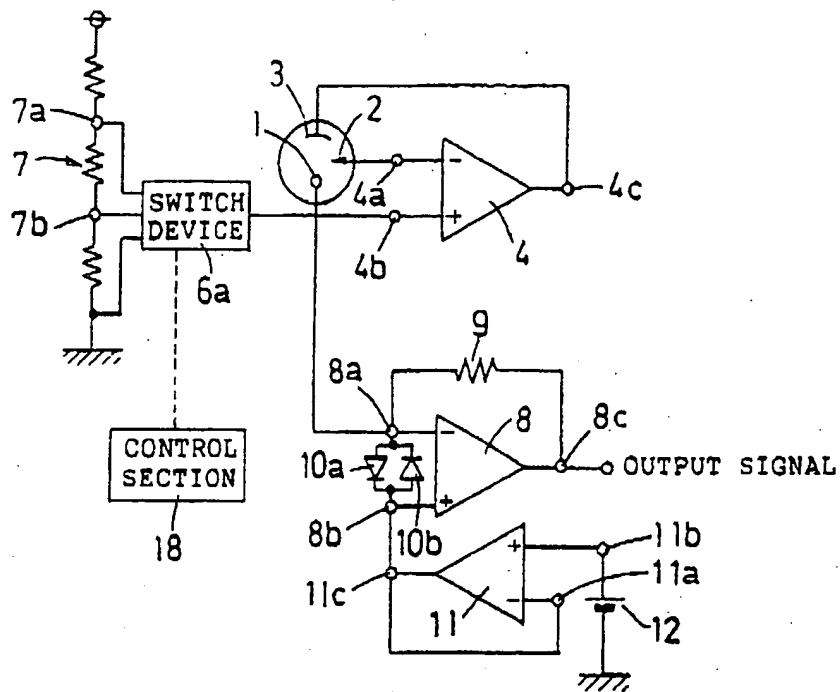
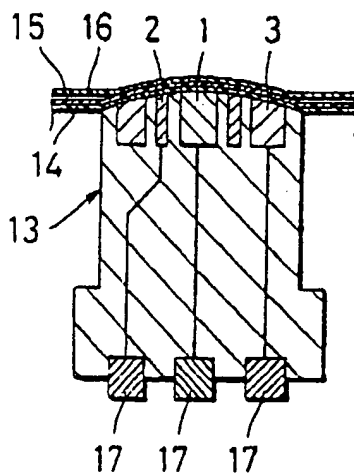


Fig.2



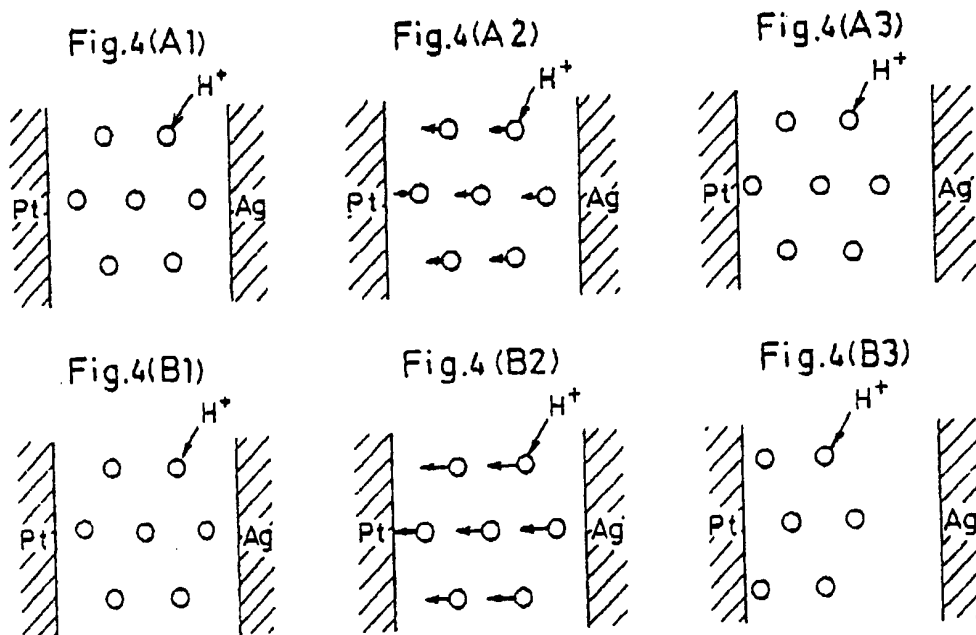
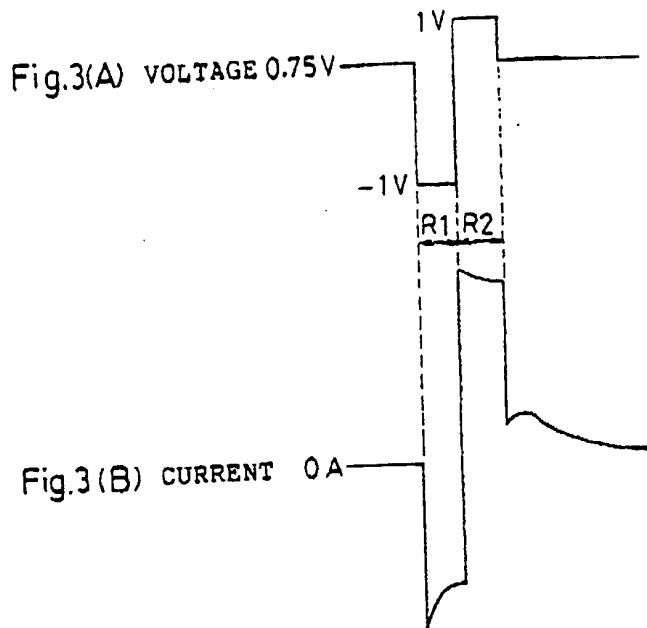


Fig. 5

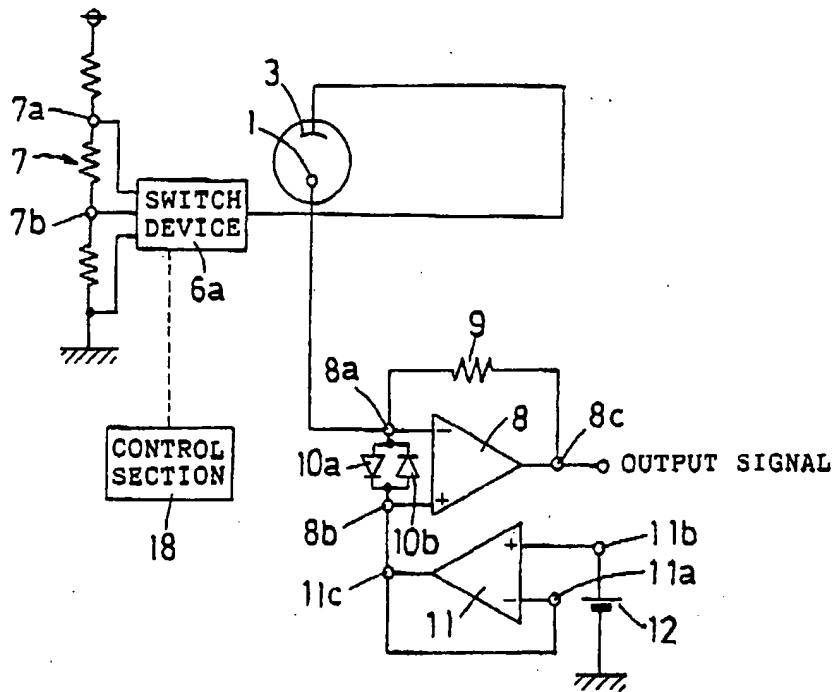
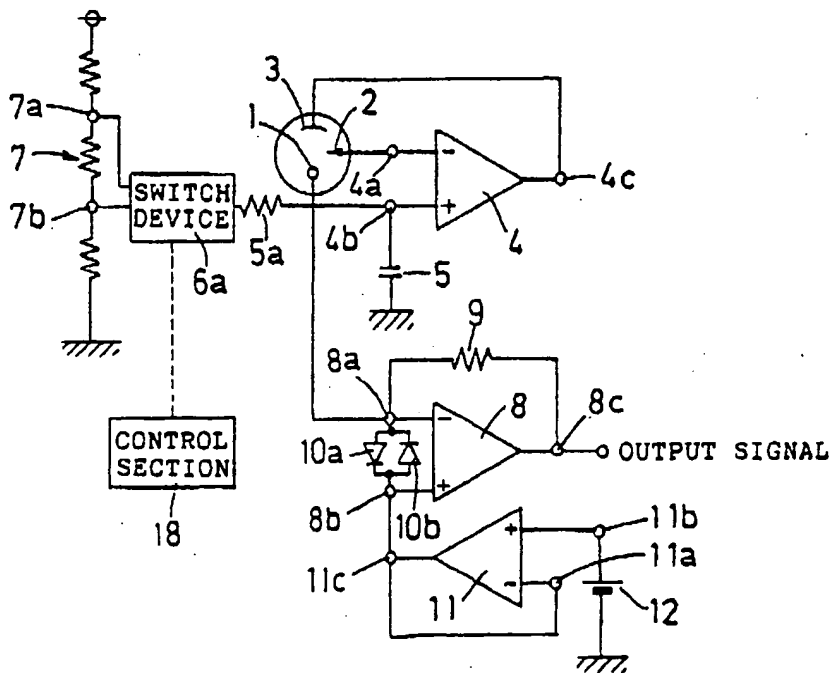


Fig. 6



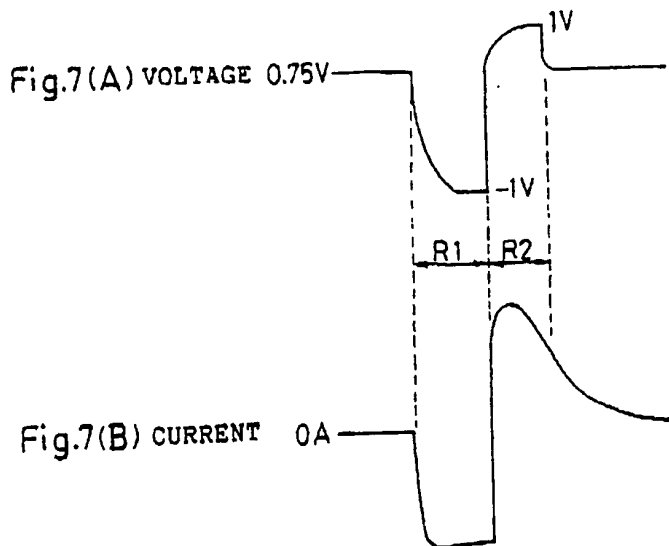
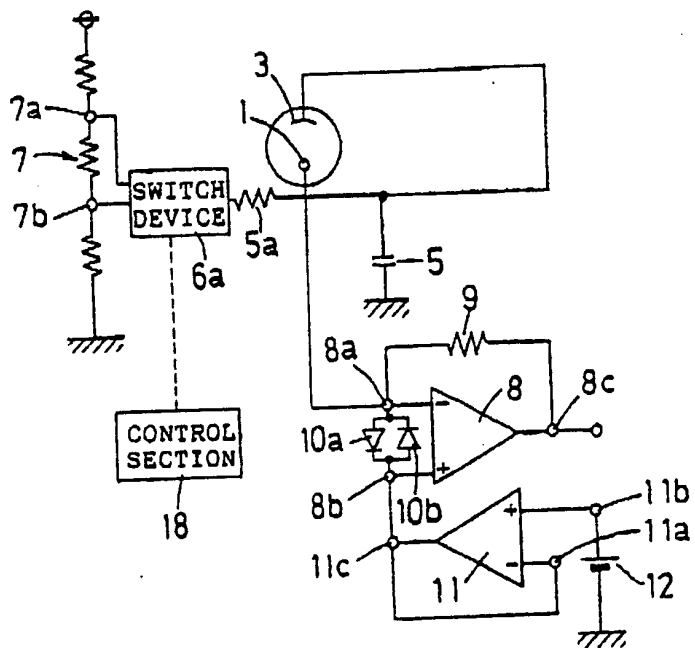


Fig.8





| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|---|---|--|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
| X | GB-A-2201248 (IMPERIAL CHEMICAL INDUSTRIES PLC) * page 9, line 1 - page 11, line 14; claims 1-11 * | 1-9 | G01N27/38 |
| X | GB-A-2019580 (SIEMENS AKTIENGESELLSCHAFT) * claims ; figures * | 1-9 | |
| X | EP-A-103109 (SIEMENS AKTIENGESELLSCHAFT) * claims 1-7 * | 1-5 | |
| A, D | PATENT ABSTRACTS OF JAPAN vol. 9, no. 329 (P-416)(2052) 24 December 1985, & JP-A-60 155959 (MATSUSHITA DENKO K.K.) 16 August 1985, * the whole document * | 1-5 | |
| | | | TECHNICAL FIELDS SEARCHED (Int. Cl.5) |
| | | | C12M G01N |
| The present search report has been drawn up for all claims | | | |
| Place of search THE HAGUE | | Date of completion of the search 23 OCTOBER 1990 | Examiner EPAILLARD P. J. H. |
| CATEGORY OF CITED DOCUMENTS | | I : theory or principle underlying the invention F : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document | |
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